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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,223	01/24/2001	Raoul E. Benveniste	015280196310	2782

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,223	BENVENISTE ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,40,41,44 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17, 40, 41, 44, and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the amendment dated 04 March, 2005. Claims 17, 40, 41, 44, and 47 are pending in the instant application.

35 U.S.C. § 112, Second Paragraph

The previous rejection of claims 17, 40, 41, and 44 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby withdrawn in response to applicants' amendment.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 17, 40, 41, and 44 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). The claims have been amended to include specific

concentrations of virus (e.g., 10 femtograms to 1 picogram). Page 13 of the disclosure references these values in terms of the p24 antigen concentration, not the concentration of virus. The disclosure teaches that 100 picograms of p24 antigen corresponds to approximately 100 infectious HIV viruses per ml. However, these concentrations do not refer to the actual viral concentrations. Appropriate amendment of the claim language is suggested (i.e., administering viral compositions comprising 100 picograms of p24 antigen; administering viral compositions comprising 100 infectious viruses/ml).

Enablement

Claims 17, 40, 41, 44, and 47 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward **methods of vaccinating humans** against HIV infection by administering an immunogen comprising an attenuated form or inactivated form of HIV, wherein said attenuation is in the *gag* coding region, that induces a protective or therapeutic immune response. Additional limitations specify that the immunogen must induce a cell-mediated immune response without inducing an "offsetting" humoral response. As previously set forth, the terms vaccine, vaccinate, and vaccinating all have an art-recognized definition and refer to an immunogenic preparation capable of inducing a protective or therapeutic immune response (see Dorland's Illustrated Medical Dictionary, 1988, and Stedman's Medical Dictionary, 1982). Thus, the claimed immunogenic composition used to vaccinate said human must provide some sort of protective or therapeutic immune response that prevents HIV infection or ameliorates the clinical sequelae associated with HIV infection.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide any guidance pertaining to the correlates of human protection. To date, the correlates of protective immunity remain to be elucidated. It is not known if neutralizing-antibody, CTL responses, or both humoral and cell-mediated immune responses are required for protection. The specificity and titer of the immune response required for protection has yet to be identified. Accordingly, the skilled artisan cannot reasonably predict if any putative vaccine composition will be protective in vivo. Although, numerous neutralizing-antibody and CTL epitopes have been identified, however, it is not known which components of the immune response are necessary and sufficient for protection from natural infection. Nothing in the specification addresses this critical issue.

2) The disclosure fails to provide any guidance pertaining to the quasispecies nature of HIV infection. The human immunodeficiency viruses exist as a genotypically/phenotypically complex group of viruses within the same host. It has been estimated that between

10^5 and 10^6 variants are present in any given individual. Viral variants are present in different tissue types, as well as, different locations within the same tissue type. Each variant possesses its own pathogenic properties. This vast genetic variation leads to immune escape and evasion. Any vaccine strategy must take the extraordinary sequence variability and mutation rate of HIV into consideration. However, the specification is silent concerning this caveat.

3) The disclosure fails to provide any guidance pertaining to the factors governing the pathogenesis of HIV-induced disease. The immunopathogenesis of HIV infection is exceedingly complex. Several mechanisms have been proposed to explain disease progression including direct pathogenic effects of the virus, HIV-induced autoimmune responses, and HIV-induced T-cell apoptosis. Non-neutralizing antibodies have been shown to enhance HIV infection. The molecular mimicry of host proteins appears to play a role. Viral peptides have are also capable of suppressing immune cell function. Thus, the choice of immunogen needs to be carefully considered before any putative vaccine is tested. Once again, the disclosure fails to provide any direction concerning these issues.

4) The disclosure fails to provide sufficient guidance from an art-recognized animal model of HIV vaccine development. One of the major obstacles confronting HIV vaccine development is the lack of a suitable animal model that accurately predicts human vaccine efficacy. While different macaque models are useful for studying immune responses, nevertheless, the numerous structural differences between HIV and SIV preclude the direct translation of macaque vaccine studies to humans. Moreover, the skilled artisan must carefully evaluate any given animal model vaccine study to ensure that suitable challenge viruses are employed. Finally, most animal models fail to test the same vaccine construct or immunogen that will be employed in human studies. Thus, these models are of

limited utility. As Feinberg and Moore (2002) conclude, "Animal models cannot determine whether a vaccine will be effective against HIV-1 infection in humans; only Phase III trials in humans can do so."

5) The disclosure fails to provide adequate guidance pertaining to the ability of any given immunogen to induce a cell-mediated immune response without generating a noticeable humoral response. The claimed invention appears to require the induction of a viral-specific CTL response without generating an appreciable antibody response. The claims require an attenuated or inactivated HIV immunogen. It has been well-documented that HIV contains both humoral and CTL epitopes. Moreover, during the course of natural infection, both neutralizing antibody and CTL responses are observed. Thus, it is not readily manifest how applicants intend to induce a CTL response by administering an attenuated or inactivated virus without inducing an antibody response. The disclosure fails to provide any evidence or publications that address this concern. As previously noted, a recent publication (Shearer and Clerici, 1997) clearly noted that Athe conditions under which some of these parameters result in a preferential response of one type or the other have not yet been determined.≅ There are several factors governing the immune response to any given immunogen (i.e., immunogen dose, adjuvant selection, route of immunization, structure of immunogen, type of antigen presenting cells, costimulatory signals, vaccinee genetic background, cytokine environment, vaccinee immunologic status) thereby making the immunization process an empirical one at best. Since all of these factors can influence the immune response, the skilled artisan cannot readily predict how any given putative vaccine will influence the immune response. Extensive testing will be required to ascertain which of the aforementioned parameters are most important. Unfortunately, the disclosure fails to address this

point as it applies to humans and putative HIV vaccines.

6) The disclosure fails to provide adequate guidance pertaining to the nature of the immunogen. It has been well-documented in the field that one of the primary problems with HIV vaccine development is that investigators do not know which immunogens, adjuvants, and immunization regimens will produce a protective or therapeutic immune response. The disclosure clearly fails to address any of these issues. This is not surprising considering that the correlates of protective immunity pertaining to HIV-1 infection have not been determined.

7) The state-of-the-art vis-à-vis HIV vaccine development has encountered many difficulties and failures (Hoth *et al.*, 1994; Stott and Almond, 1995; Graham and Wright, 1995; Haynes *et al.*, 1996; Haynes, 1996; Kent *et al.*, 1997; Lee, 1997; Letvin, 1998; Burton and Moore, 1998; Moore and Burton, 1999; Nathanson and Mathieson, 2000; Johnston, 2000; Bende and Johnston, 2000; Feinberg and Moore, 2002). To date, there is no effective vaccine for the prevention or treatment of HIV-1 or -2 infection. Various vaccines that displayed promising results in macaque models have undergone preliminary clinical trials. None of these vaccines have proved efficacious. This is due to a number of factors including the *quasispecies* nature of HIV infection which leads to rapid immune escape, a lack of understanding of the correlates of protective immunity thereby precluding the identification of suitable viral immunogens, delivery vehicles, and immunization regimens, the lack of suitable animal models in which to assess vaccine efficacy, the ability of the virus to reside in quiescent T-lymphocytes thereby persisting indefinitely, and a lack of understanding of mucosal immune responses. The disclosure fails to provide any illumination on any of these topics.

8) The claims are of considerable breadth and encompass any given immunogen without providing sufficient structural and functional

guidance. The generic claims simply require an inactivated or attenuated HIV. The HIV genome is approximately 9.5 kb in length and encodes various structural and regulatory genes. Since the precise immunogen and form that are required to produce a therapeutic or protective immune response remain to be elucidated, the skilled artisan has been asked to guess as to which regions of the genome should be modified to produce a suitably attenuated virus. Moreover, problems with attenuated vaccines include reversion to a more virulent form, even with multiple gene deletions. Considering the unpredictability of the state-of-the-art vis-à-vis HIV vaccine development the skilled artisan would reasonably conclude that the disclosure fails to support the breadth of the claimed invention.

9) The disclosure fails to provide any working embodiments. As noted supra, there are several complications associated with HIV vaccine development. Accordingly, the skilled artisan would reasonably require a working example before practicing the claimed invention. The disclosure is merely prophetic and fails to provide any actual working embodiments.

Thus, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Response to Arguments

Applicants assert that the disclosure provides the correlates of human protection. It was asserted that cell-mediated immunity provides protection. This argument is not convincing in view of the large number of failed HIV vaccine trials and publications stating that the correlates of protection remain to be elucidated. It was further argued that the vaccine of interest need not protect against sundry HIV viral isolates. The reason this concern was raised is because the plasticity, or quasispecies nature, of the

HIV genome leads to rapid immune escape. Thus, a vaccine needs to provide long-lasting immunity, not just a brief immune response. The disclosure and response fail to provide any objective scientific data that addresses this concern. Third, applicants assert that the issues raised by the examiner fall within the purview of the Food and Drug Administration. The examiner does not share this assessment. Applicants are reminded that considerations made by the FDA for approving the licensing of vaccines for clinical use are different from those made by the PTO in determining the enablement of a claim. *Scott* v. *Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994). The legal requirements governing enablement determinations are clearly set forth in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). These were the criteria applied by the Examiner in formulating the rejection. Applicants are invited to provide objective scientific data or appropriate publications that address these caveats. Fourth, it was argued that the examiner is requiring data from a phase III clinical trial in support of enablement. No such requirement has been made by the office. However, applicants are directed toward *Ex parte Balzarini*, 21 U.S.P.Q.2d 1892 (U.S.P.T.O. Bd. Pat. App. Int., 1991), which involved HIV-1 therapeutics. The Board agreed with the examiner's assessment that existing *in vitro* tissue culture assays and *in vivo* animal models were not predictive of clinical efficacy. While the court did not state what type of rebuttal evidence would be appropriate, they nevertheless suggested that in highly unpredictable fields such as HIV vaccine and therapeutic development, some clinical testing might be required. Applicants have failed to provide any objective scientific data addressing this caveat.

Applicants further argue that sufficient guidance has been provided concerning the nature of the immunogen. The claims now

recite a completely inactivated or attenuated virus simply lacking a portion of the *gag* NC gene. However, the claims fail to provide any other salient characteristics concerning the presence or absence of other attenuating mutations or the nature of inactivation (i.e., chemical treatment). Moreover, it has been well-demonstrated in the HIV vaccine art that even multiply attenuated HIV/SIV constructs are not truly attenuated, but are simply replication-immpaired. It has also been demonstrated that various gene deletions can be repaired by the virus *in vivo*. Applicants further assert that the references relied upon to define the state-of-the-art actually support the claimed invention. This argument is illogical since the state-of-the-art clearly illustrates that numerous HIV vaccine approaches have failed for the reasons discussed. Applicants' response fails to provide any objective evidence that would lead the skilled artisan to conclude that the claimed invention would provide a protective or therapeutic immune response. Finally, it was argued that the macaque model described and addressed in the previously submitted declaration of Dr. Benveniste provides a sufficient working embodiment. The declaration was addressed in the last office action. Contrary to applicants' assertion, the macaque model is NOT predictive of clinical efficacy (see the various documents cited above). Accordingly, the rejection is proper and hereby maintained.

Finality of Office Action

Applicants' amendment necessitated any and all new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL. THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION**

AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access

to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

30 May, 2005